^{177}Lu-BPAMD – from bone imaging to therapy with a macrocycle-bisphosphonate ligand

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Introduction: ^{68}Ga-BPAMD (BPAMD = (4-{[bis-(phosphonomethyl))carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl)acetic acid) was used in a first human *in vivo* study for diagnosis of osteoblastic bone metastases. The DOTA-based bisphosphonate ligand BPAMD may also be suitable for complexation with therapeutic radionuclides such as ^{177}Lu. The same ligand thus may be used for diagnosis, dosimetry calculation, therapy and therapy control via PET.

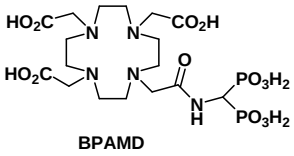

Figure 1: Ligand BPAMD used for labelling with ^{177}Lu

Experimental: ^{177}Lu was provided in 0.04 M HCl via the ^{176}Yb(n,γ)^{177}Yb → ^{177}Lu production process. The radiolabelling was optimized using different amounts of ligand in acetate buffer solution at pH 4-5 and different temperatures of 25 – 95 °C. For quality control different radio-TLC systems were used (Silica TLC plates or ITLC strips with citrate buffer at pH 4). The stability of ^{177}Lu-BPAMD was investigated for a period of one week.

Results: BPAMD can be labelled in almost quantitative radiochemical yield using about 100 nmol of BPAMD in less than 30 min in acetate buffer solution at 90 °C. ^{177}Lu-BPAMD shows radiolysis within hours under high activity concentrations of 15 GBq/mL. Generally, radical scavengers such as ethanol or gentisic acid can be applied to suppress radiolysis. However, ethanol alone could not sufficiently preclude the radiolysis here. Therefore, the product solution was dilution directly after labelling and by an addition of gentisic acid the degradation could be minimized to only 1-2% within 24h. These findings were further transferred towards a protocol for human application and endoradiotherapy with ^{177}Lu-BPAMD. Two patients with bone metastases were treated with 5 GBq of ^{177}Lu-BPAMD each and monitored by SPECT over 24h. Both showed significant enrichment of the radiotracer on bone lesions.

Conclusions: BPAMD exhibits the potential to be used for diagnosis and therapy monitoring (by means of PET with ^{68}Ga) and radionuclide therapy itself (with ^{177}Lu). The uptake is reflecting the farnesyl diphosphate synthase enzyme dynamics in the HMG-CoA reductase pathway. Since this pathway is mainly responsible for the osteoclastic bone destruction, BPAMD is a promising ligand for ^{177}Lu-therapy of bone lesions.

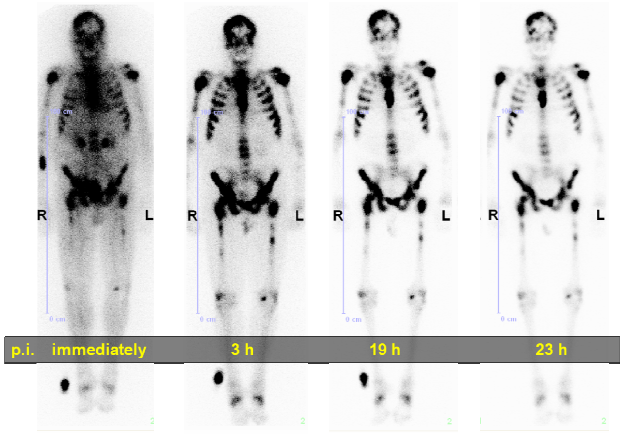

Figure 2: ^{177}Lu-BPAMD SPECT (5 GBq) showing intense accumulation of tracer in multiple osteoblastic lesions and fast clearance from blood pool. 19h post injection almost no background is visible.

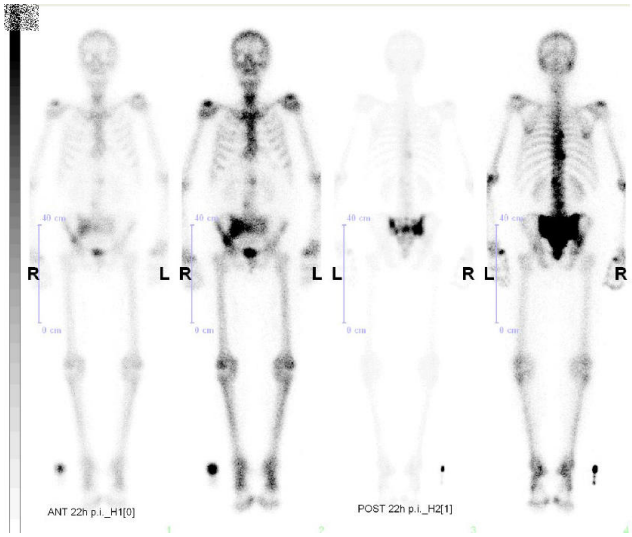

Figure 3: Second patient treated with ^{177}Lu-BPAMD shows 22h post injection also high accumulation of the therapeutic agent in bone lesions, whereas in the rest of the skeleton there is only very low radioactivity detected.

References

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